HERPES SIMPLEX AND HERPES ZOSTER KERATOUVEITIS: DIAGNOSIS AND MANAGEMENT*

DEBORAH PAVAN-LANGSTON, M.D.
Eye Research Institute of Retina Foundation and Cornea Service
Massachusetts Eye and Ear Infirmary
Boston, Mass.

KERATOUVEITIS may be associated with almost any acute viral infection of the anterior ocular segment. In the case of adenovirus or vaccinial disease, however, uveal involvement is rare and usually is secondary to inflammation in the cornea. Such inflammatory disease ususally does not recur and subsides when the acute keratitis subsides. The keratouveitides of herpes simplex and herpes zoster, however, are of much greater concern to the physician because both not only may pose complicated clinical problems but tend to recur chronically as keratitis, iritis, or both. Diagnosis and therapy of these two ophthalmic diseases become much more complicated in the long run. The variety and extent of the pertinent literature are equally complex. I shall review some current concepts in the diagnosis and management of herpes simplex and herpes zoster keratouveitis.

Herpes Simplex Ocular Disease

Almost 300,000 cases of this ophthalmic disease occur yearly in the United States, and physicians are justifiably concerned about appropriate treatment for this often baffling infection. To understand the advantages and disadvantages of the many drugs used in treating ocular herpes it is necessary to understand not only the effects of the drugs themselves but the

*This review is based in part on Pavan-Langston, D. and Abelson, M.: The Role of Steroids in Ocular Herpes. In: *Controversies in Ophthalmology*, Boruchoff, S. A., Hutchinson, B. T., and Brockhurst, R., editors. Philadelphia, Saunders, 1976; and Pavan-Langston, D.: Varicella Zoster of the Anterior Segment. In: *Proc. Second World Cornea Conf.*, Lemp, M. et al., editors. Boston, Little, Brown, 1976.

This research was supported in part by Public Health Service Research Grant EY-00208 from the National Eye Institute, Bethesda, Md.; A William Friedkin Scholarship from Research to Prevent Blindness, Inc., New York, N.Y.; The N. and V. Johnstone Fund, Boston, Mass., The A.N. Prince Trust, Chicago, Ill., and the Massachusetts Lions Eye Research Fund, Inc., Boston, Mass.

Address for reprint requests: Eye Research Institute of Retina Foundation, 20 Staniford Street, Boston, Mass. 02114.

various forms and pathogenesis of this multifaceted disease. Ocular herpes itself may be classified as primary or recurrent.

Primary Herpes

Primary disease is an acute keratoconjunctivitis with or without cutaneous involvement in a nonimmune host caused by live, infectious *Herpes simplex* virus. In the immunologically competent host the vesicular eruption remains fairly well localized as a self-limited condition which resolves entirely without scarring and usually without specific treatment.

Recurrent Herpes

This is a disease of a previously exposed host who has both celluar and humoral immunity. It may occur as one or a combination of the following:[1,2] epithelial infectious ulcers, epithelial trophic ulcers (metaherpes), stromal disease—either viral interstitial or disciform keratitis, and iridocyclitis.

1) *Epithelial infectious ulcers.* Dendritic, dendrogeographic, or geographic ulcerations of the cornea are caused by live virus. Van Horn et al. have reported little inflammatory cell reaction (polymorphonuclear leukocytes with no β-lymphocytes) in this disease, but many free virus particles lying in intracellular and extracellular locations, particularly in the basal epithelium.[3] With antiviral chemotherapy arresting viral replication until infected cells slough from the eye or with debridement alone, the infectious epithelial disease resolves 80 to 90% of the time without complication and without need for anti-inflammatory drugs. Limbal ulcers are more resistant to healing, but eventually close without much scarring.

Indeed, as in primary herpes, the use of steroids in infectious epithelial disease serves only to make the ulceration spread and to prolong the infectious phase of the disease.[18] As Meyer et al. have shown, this is caused in part by local inhibition of antibody-forming cells (β-lymphocytes) in the cornea and uveal tract.[4] Because there is no effect on the number of β-lymphocytes in the regional lymph nodes or on circulating antibody response, the host is still capable of immune reaction once inflammation-inhibiting steroids are removed. Higher titers of corneal viral antigen gain access to deeper tissues and subsequently activate the antibody-complex reaction. Further evidence that topical steroids enhance deep penetration of surface virus and make the eye more vulnerable to stromal and uveal inflammatory reaction is provided by Robbins and

TABLE I. RULES FOR JUDICIOUS USE OF STEROIDS

1)	Always cover topical steroids with a prophylactic antiviral agent to prevent epithelial reinfection unless dose is below prednisolone 1/8% daily.
2)	Never use topical steroids in herpes simplex dendritic or geographic ulcers in the absence of stromal disease.
3)	Never discontinue steroids abruptly. Look for corneal steroid addiction.
4)	During steroid treatment, eyes should be watched for signs of bacteria or fungal superinfection.
5)	Always use the lowest dose of steroid that will control inflammatory disease.
6)	Use steroids in interstitial keratitis affecting the visual axis and in anticipation of keratoplasty or disciform iritis damaging the endothelium.

Galin, who demonstrated that these drugs actively enhance transfer through the cornea of large molecular-weight structures similar to herpes virus.[5]

2) *Epithelial trophic or metaherpetic ulcers* are frequently confused with infectious geographic ulcers because of their nondescript appearance and ovoid shape. They are, in fact, mechanical healing problems similar to recurrent traumatic erosion and are believed to be caused by damage to the basement membrane sustained during the acute infectious epithelial stage.[6] Normal epithelial cells do not interdigitate with their basement membrane but are attached by election-dense hemidesmosomes and tonofibrils. If the basement membrane is damaged it heals extremely slowly and epithelial cells are unable to maintain their position after migrating across the bed of the ulcer. They are knocked off repeatedly by lid motion, which ultimately results in a breakdown over a recently healed or partially healed dendritic or geographic ulcer which was formerly (but is no longer) infected with herpes. Trophic ulcers are characterized by greyish, heaped-up edges, by indolent behavior and, in pure form, by sparse inflammatory component. Because of the mechanical nature of the problem, treatment tries to protect the damaged basement membrane by use of patching, a soft contact lens, or, occasionally, a conjunctival flap. In the absence of underlying stromal inflammatory disease which may interfere with healing of the basement membrane, anti-inflammatory therapy by glucocorticoids is usually not needed (see below).

3) *Stromal disease*. With management of stromal disease or uveitis one locks horns with the do's and don'ts of steroids in ocular herpes (Table I). Animal studies have demonstrated the spontaneous spread of virus to the stroma and endothelium without the aid of steroids.[7] This spontaneous

deep spread of a more virulent virus, or the steroid-aided penetration of any herpes virus, has the same effect—that of deep antigen against which the body will muster potentially destructive inflammatory defenses. The clinician, therefore, may contemplate treating deep disease which threatens vision with glucocorticoids even in the absence of previous steroid treatment.

Like ocular herpes in general, stromal disease can be divided into two categories: viral interstitial and "disciform."

Viral interstitial keratitis (IK) presents as necrotic, blotchy, cheesy-white infiltrates which may lie under ulcers or may appear independently. It is important, and occasionally difficult, to distinguish these from secondary bacterial or fungal infections, which are much less indolent. This clinical pattern is associated with intact virus in the stroma.[8,9] After several weeks of smoldering, dense leashes of deep neovascularization begin to move in as though in pursuit of the infiltrates. These may be small and focal or severe enough to give the cornea a red and white mottled pattern on gross inspection.[8,9] Probably no form of herpes is more diffcult for a physician to follow without steroid therapy than herpetic IK, and whether these drugs are used depends on surgical plans for the eye and the severity of the general ocular reaction and its associated corneal edema. In the absence of steroid therapy, antiviral drugs are not indicated.

If the infiltrates do not involve the visual axis, steroid treatment is not indicated. The process burns itself out spontaneously in weeks to months and leaves some—but often amazingly little—scarring, even after rather severe involvement. Neovascularization regresses to leave barely visible "ghost vessels." An overlying irregular astigmatism will often smooth out. Generally, if steroids have never been used in an eye infected with viral IK, one should try to ride out the course of disease without them. As noted, this form of keratitis is thought to be caused by live virus, the spread of which may be aided by glucocorticoids. In this situation therapy probably is best confined to antiviral agents several times daily, mydriatics if needed for associated iridocyclitis, and artificial tears to lubricate a potentially compromised epithelium.

However, if the inflammatory reaction becomes severe, if steroids have been used previously, if the visual axis is threatened, or if future transplant surgery is contemplated, steroids will control the inflammatory reaction and decrease formation of scar tissue and invasion by deep vessels which would later compromise the success of a graft. The minimum cortico-

steroid dose needed to control the disease ranges from 0.1% dexamethasone every three hours to 0.12% prednisolone every other day. Once hyperemia and edema begin to wane, steroids should be tapered downward over several weeks to several months. Concomitant prophylactic antiviral agents, e.g., idoxuridine or vidarabine ointment four times daily, and antibiotics such as polymyxin-neomycin ointment twice daily are important and should be continued until the dose is reduced to the equivalent of 0.2% prednisolone once daily or less frequently. If the process reactivates after a dose reduction, steroids should be increased to the previous level for a longer time and attempts to reduce dosage should be resumed as the process ultimately burns out. Currently available antiviral agents have no proved effect on stromal keratitis per se. Keratoplasty should be deferred until the eye has been quiet with little or no steroid treatment for several months because viral IK is the form of ocular herpes most likely to recur in a new graft.[10]

Disciform keratitis is the well-known second form of stromal disease. This form most frequently follows improper use of steroids in treating dendrite or geographic ulcerative keratitis, but may also result from spontaneous penetration of viral antigen. The exact cause of disciform keratitis is not completely understood, but it is now believed that both immune mechanisms and lingering toxic effects from the original viral invasion contribute to this form of keratitis. Antigenic alteration of the surface membrane of corneal cellular elements such that the body regards them as foreign and the antigenically active residue of viral particles both cause the body to respond by sending inflammatory cells. This delayed hypersensitivity reaction is characterized by sensitized lymphocytes, plasma cells, and, ultimately, macrophages and polymorphonuclear leukocytes.[11-14]

In its most benign form, disciform keratitis is clinically manifested as focal, disc-shaped stromal edema without necrosis or neovascularization. Keratic precipitates composed of lymphocytes and plasma cells may cling to the endothelium exactly in the area of disciform edema. That iritis is absent in milder cases suggests that the keratic precipitates are especially attracted to focal deposits of corneal antigen.

In moderate disciform disease more diffuse edema and folds in Descemet's membrane are seen frequently, indicating that the toxic inflammatory reaction compromises the endothelium and that fluid enters the cornea in abnormally great amounts. Vessels are often present. The most severe forms of disciform keratitis produce the most destructive effects of

uncontrolled inflammatory reaction in the cornea, with diffuse edema and, frequently, ulcerating bullous keratopathy with necrotic stromal thinning, melting, neovascularization, and severe iritis. Patches of white viral IK may be seen scattered in these corneas.

The same rules apply to the treatment of disciform keratitis as in viral IK. If a patient has never been treated by steroids and the disease is mild, every effort should be made to avoid these drugs. Because the disease is an immune reaction, unlike IK, antiviral agents have no role except as prophylaxis against reactivation of epithelial infection. Patients are more comfortable with cycloplegics because they usually have mild iridocyclitis. Artificial tears and dark spectacles may help the patient through a difficult period until the reaction subsides. Usually little or no scarring occurs.

The eye with moderate or severe disciform keratitis needs the anti-inflammatory, antiscarring, antineovascular effects of the glucocorticoids. In the presence of a notable antigen-antibody reaction in the stroma, with its associated immune cellular invasion and release of lysosomal enzymes, neighboring endothelium may be damaged irreversibly unless it is protected by steroids. If unchecked, the inflammatory reaction will increase scarring and promote deep neovascularization which not only compromises the potential success of a future graft but gives circulating β-lymphocytes and humoral antibodies direct access to the deeper and central areas of the cornea. The vessels potentiate disciform disease and make another immune reaction more likely, even if the present one resolves.

The physician should prescribe the minimum dose of glucocorticoid which will control the reaction, followed by gradual (never abrupt) tapering dosage, and, if possible, cessation of treatment. A typical regimen includes 0.1% dexamethasone every three hours for a few days then every six hours, three times daily, twice daily, daily, every other day, and so forth—each regimen for a few days or weeks at a time. An alternative method uses progressively decreased strengths of glucocorticoid, such as starting with 1% prednisolone every three hours for severe disease and working down through stepwise fashion:[15]

1% → q. 3 h. →q. 6 h. →t.i.d. →b.i.d. → q.d
0.2% q.i.d. → (little change from 1.0% q.d.) → t.i.d. → b.i.d. → q.d. → q. 2 d. → q. 3 d. to cessation

Less severe disease would warrant starting with lower levels of steroid therapy.

Too abrupt cessation of steroids may result in recrudescence, and steroid dosage temporarily will have to be increased. Occasionally, patients will never be able to stop steroids completely without recurrence of disease and may require very small doses once or twice weekly. Until the dosage is reduced to once daily or less frequently at the equivalent of 0.2% prednisolone, prophylactic antiviral agents and antibiotics should be used once or twice daily. Although steroids do not increase recurrence of infectious disease, they enhance the progression of infection should it occur.[14] Cycloplegics may be discontinued when the anterior chamber is clear or the patient may be given short-acting mydriatic at bedtime, because daytime photophobia may be quite uncomfortable.

4) *Combined epithelial and stromal disease.* Frequently, a patient presents with combined disciform disease and an infected epithelial ulcer or a noninfected trophic healing defect. In the former case, gentle debridement and antiviral therapy should be started at least a day or two before steroids. If the ulcer progresses despite topical steroid therapy, the frequency or strength of dosage should be reduced until the ulcer is under control and is healing. Systemic steroids alone are of little use in corneal disease because negligible titers of these drugs are attained.

If disciform keratitis is combined with trophic ulceration or if the original infected ulcer becomes trophic in nature, control of underlying stromal edema with steroids and the application of a very thin, soft-contact lens will aid healing. However, the longer an epithelial defect persists, especially in men, the greater are the chances of collagenase release and melting.[16] Steroids may enhance this release and contribute to ultimate corneal perforation. Surgical intervention to construct a conjunctival flap or penetrating keratoplasty may then be necessary.

5) *Iridocyclitis.* Herpes simplex virus may cause recurrent iridocyclitis and, on occasion, panuveitis.[17] Intraocular inflammation may occur before known infection or without concomitant active keratitis, but it almost invariably accompanies active keratitis, and may be caused by specific involvement by the virus or may be secondary to irritative effects of the keratitis. Uveitis in an eye with previous herpetic keratitis should be considered herpetic until proved otherwise by examination or laboratory tests.

The exact etiology of this uveitis is not entirely clear. Intact virus particles are known to be present in the aqueous humor in a significant number of patients, and, in one patient, in a retrocorneal membrane.[18,19] An immune inflammatory component also is involved.

Treatment is nonspecific. Topical antiviral agents do not penetrate enough to achieve therapeutic titers.[20-23] Systemically administered vidarabine appears to have some therapeutic effect but this experimental therapy is not yet established.[23] Suppression of the inflammatory reaction remains the best method available, although it is far from ideal. If a patient has never been treated by steroids, every effort should be made to avoid them. Cycloplegic mydriatics and nonsteroid anti-inflammatory drugs such as indomethacin 25 mg. three times daily or aspirin 600 mg. four times daily may help to avoid structural alteration of the eye. If the reaction persists and is more than a mild, asymptomatic cell-and-flare reaction and threatens synechial formation or if the patient has been treated only with steroids previously, topical steroids should be reinstituted, using a regimen similar to that for disciform keratitis. The initial dose and frequency of steroid should be compatible with the severity of the disease and prophylactic antiviral and antibiotic agents should be used with the usual cycloplegic mydriatic drugs.

If ulcerative keratitis is present, particularly if the cornea is melting, systemic steroids such as oral prednisone, 25 mg. two or three times daily with meals, may be substituted for part or all of the topical steroid regimen. Systemic steroids reach the uveal tract but not the cornea in therapeutic titers. Concomitant topical medication should be continued as before.

KERATOPLASTY

Use of steroids in managing keratoplasty for herpes simplex keratitis has been the subject of less controversy, but still perturbs many clinicians who fear recurrence of infection in the graft. Langston et al. evaluated corticosteroid treatment in herpetic keratoplasty, [23] and showed that whether the patient used 0.1% desamethasone less than once daily or as frequently as every four hours, the recurrence rate of dendritic disease in the graft was the same, 15%. Postoperative complications such as wound synechiae, graft rejection, and secondary glaucoma were more frequent in low-steroid groups, and the incidence of wound dehiscence in the high-dose corticosteroid group was negligible. The over-all success rate of penetrating keratoplasty in herpes (80%) appears to be related to the use of high doses of steroids in the immediate postoperative period (up to three months). Their use is unquestionably indicated.

TABLE II. JUDICIOUS TREATMENT OF HERPES SIMPLEX OCULAR DISEASE

Nature of herpetic involvement	*Treatment*
Primary herpes	IDU or vidarabine for any corneal lesions, Betadine ointment and warm compresses for skin lesions
Lid	Prophylactic IDU or vidarabine
Epithelial dendritic or geographic corneal ulcer	IDU, vidarabine, debridement (never steroids)
Limbal epithelial ulcer (usually slow to heal)	IDU or vidarabine; steroids not indicated
Trophic postinfectious epithelial ulcer (metaherpetic)	Patch, soft contact lens, conjunctival flaps, debride overhanging edges
Stromal interstitial keratitis	IDU or vidarabine; steroids in low doses topically if there is impingement on optical axis
Stromal disciform keratitis	Dilate (antibiotic-antiviral umbrella for steroids); use steroids if any signs of endothelial decompensation commence
Iritis (iridocyclitis)	Systemic steroids and topical antivirals; dilate if associated keratitis, do not overtreat minimal cells and flare unless endothelial decompensation is present

IDU = idoxuridine

In brief, antiviral agents, antibiotics, glucocorticoids, and cycloplegics all have definite roles in ocular herpes. The physician must understand the beneficial and potentially harmful effects of the drugs themselves, and the pathogenesis of the various forms of this disease. Judiciously used, these drugs frequently prevent visual loss by eliminating the virus, preventing secondary bacterial infection, and decreasing irreversible inflammatory alterations of the cornea and uveal tract in herpes simplex keratouveitis (Table II).

Herpes Zoster Ophthalmicus

Herpes zoster, otherwise known as shingles, zona, or acute posterior ganglionitis, causes about 1% of all dermatolgical disease, of which 7% is ophthalmic and may be divided into two not always distinguishable categories: primary (infectious) and secondary (symptomatic). Primary zoster is an acute infection of a dorsal root ganglion by the virus of chickenpox.

Secondary or zosteriform eruption may follow ganglion involvement by any form of inflammatory or neoplastic process, and may be associated with tuberculosis, syphilitic, leukemic, or lymphatomatous infiltrates, and postirradiation neuritis. Both primary and secondary disease are characterized by vesicular skin lesions distributed over the sensory dermatome innervated by the affected ganglion. The associated pain and acute regional lymphadenitis help to distinguish the primary form of zoster from the secondary eruption. There is significantly higher incidence of zoster in patients with occult malignant disease.[24-28]

Pathogenesis

There are two established theories of infectious zoster: 1) reactivation of latent virus in the Gasserian ganglion, left there after a previous attack of chickenpox, and 2) reintroduction of exogenous virus through direct or indirect contact with either a chickenpox or zoster patient.[29] Both involve infection of an immunologically compromised or partially immune patient who had had previous exposure to chickenpox but who failed to develop an adequate immune response on first exposure. Because a satisfactory immune response usually develops with zoster, recurrence is extremely unlikely.

The incubation period for endogenous zoster is not known, but in cases following exposure to chickenpox, incubation varied from a few days to two weeks.[29] It typically begins with headache, malaise, fever, and chills—followed a day or two later by neuralgic pain and two to three days after this by hot, flushed hyperesthesia and edema of one or more dermatomes, which then erupt with a single or multiple crops of clear vesicles from which virus may be cultured for just three days. Vesicles then become turbid and yellow, and, unlike H. simplex, form deep eschars that may leave behind tell-tale pitted scars over the dermatome.

The acute inflammatory period lasts eight to 14 days, but skin ulcerations may take many weeks to heal and result in the equivalent of third-degree burns, with total lid retraction or ptosis and sloughing of lashes and tissue.[25-27]

Neuronal Relations

The dermatomes most commonly affected are the thoracic, followed in frequency by the cranial, cervical, and, occasionally, the lumbar or sacral.

If the first or ophthalmic division of the fifth sensory cranial nerve (Gasserian ganglion) is involved, herpes zoster ophthalmicus results. Occasionally, the second or maxillary division will be involved as well, and very rarely the mandibular.

The frontal nerve is most frequently affected. Through its supraorbital and supratrochlear branches it innervates the upper lid, forehead, and some of the superior conjunctiva. The main sensory nerve to the eyeball is its nasociliary branch, which divides in the posterior orbit into the infratrochlear and nasal nerves. The infratrochlear nerve supplies the lacrimal sac, conjunctiva, skin of both lids, and root of the nose. The nasal nerve, however, supplies the most critical structures of all, and, together with sympathetic branches from the ciliary ganglion, it innervates the sclera, cornea, iris, ciliary body, and choroid through the long short ciliary nerves and the less critical but diagnostically helpful tip of the nose through the nasal nerve proper. By direct neural connection to the many structures of the eye, both external and internal, the zoster virus causes such variable and severe diseases as cicatricial lid retraction, paralytic ptosis, conjunctivitis, scleritis, keratitis, iridocyclitis, retinitis, choroiditis, optic neuritis and atrophy, retrobulbar neuritis, Argyll Robertson's pupil, exophthalmos, partial or complete third nerve palsy, isolated pupillary paralysis, fourth and sixth nerve palsies, acute and chronic glaucoma, and even sympathetic ophthalmia.[24-28]

Clinical Disease

This paper deals with opthalmic disease of the anterior segments, which usually presents as a combination of two or more of the following: conjunctivitis and scleritis, keratitis, iridocyclitis, and glaucoma.

1) *Conjunctivitis and scleritis.* Complications in the eye itself occur in about half the cases. Conjunctival involvement is common and may take the form of watery hyperemia with petechial hemorrhages, follicular conjunctivitis with regional adenopathy, or severe necrotizing membranous inflammation. Scleritis may be diffuse, associated with keratitis or iritis, or appear as focal, elevated tender nodules during the acute disease or two to three months after the cutaneous eruption has cleared. As these resolve, scleral thinning and staphyloma formation are not unusual.[24,27,30]

2) *Keratitis.* The keratitis that occurs in about 40% of all patients assumes many forms and may precede neuralgia or skin lesions. It may be

a fine or coarse punctate epithelial keratitis with or without stromal edema, which gives the cornea a ground-glass appearance.[24-27,30] More frequently, actual group vesicle formation with ulceration, dendritic in pattern and easily mistaken for herpes simplex keratitis, occurs. Zoster has been isolated from these dendritic lesions by myself and McCulley.[31] We described two medusa-like lesions and a third zoster dendrite as grey, appearing as if painted on the surface of the cornea. The dendrites cleared rapidly following idoxuridine or steroid therapy, leaving mild anterior stromal nebulae. Piebenga and Laibson described similar lesions in 13 patients and noted that they appeared as grey, heaped up, superficial, plaquelike formations which were coarser than simplex dendrites, lacked terminal bulbs, and stained poorly with fluorescein.[32] Zoster virus did not grow from these dendrites, but the absence of serum antibodies for herpes simplex and the presence of florid zosteriform dermal involvement strongly supported the diagnosis of zoster dendritic keratitis.

In keratitis corneal sensation usually is much reduced, but in herpes zoster alone this anesthesia frequently is highly localized. A ciliary nerve may be affected exclusively, so that the disease presents as interstitial keratitis and anesthesia of a sector, the remainder of the cornea being entirely normal.[24]

Rarely, chronic serpiginous ulceration may occur, and in particularly devastating disease the entire epithelial surface of the cornea may slough. The stroma in these severe cases is diffusely cloudy and edematous to an unusual degree and epithelial healing is slow. Melting and corneal perforation may supervene in situations where neither epithelium nor vascularized pannus cover the corneal surface.

Stromal keratitis, disciform or diffuse, may occur with or independently of epithelial disease. This interstitial inflammation may smolder for months and induce neovascularization unless controlled by topical steroids. Indistinguishable clinically from herpes simplex stromal keratitis, it probably represents an immune response similar to that seen with chronic herpes simplex keratitits, but this is not certain.[24,25]

Neuroparalytic ulceration with interstitial keratitis similar to that which follows trigeminal nerve ablation may develop slowly without spontaneous cicatrization, in which case melting and perforation may ensue, or with dense neovascular pannus, which heals but severely scars the cornea. Persistent epithelial defects which threaten to melt or which actually started to melt may heal under soft contact-lens therapy. Very thin lenses,

because of their oxygen permeability, are most successful.[33] Any vascularization proceeding under the lens probably should be allowed to progress, because it may aid healing. These eyes are poor surgical risks, but it is unlikely that keratoplasty would be planned. Paralysis of the sensory root is not invariably accompanied by neurotrophic disease, however, and patients with markedly anesthetic corneas may maintain a clear stroma and epithelium.

3) *Iridocyclitis*. Other than the cornea, the anterior uveal tract is the ocular structure most frequently affected. Involvement may occur early or late and is independent of corneal activity. Iridocyclitis may be characterized by photophobia, ciliary flush, miosis, intense ocular pain, decreased vision, fine keratic precipitates, edema and hyperemia of the iris, and anterior peripheral and posterior synechiae secondary to plastic exudate.

Histopathologically, herpes zoster ophthalmicus characteristically shows plasma cell-lymphocyte infiltration of the posterior ciliary nerves and vessels, particularly in the retrobulbar tissue and uveal structures. Herpes zoster iritis is chiefly a vasculitis similar to polyarteritis nodosa, while herpes simplex iritis is primarily a diffuse lymphocytic infiltrate of iris stroma. The usual focal or sector atrophy of the iris seen in herpes zoster iritis results from localized ischemic necrosis caused by vasculitis, and resembles the ischemic necrosis observed after acute-angle closure glaucoma or excessive diathermy and muscle detachment in retinal surgery. Hypopyon, hemorrhage into the anterior chamber, iris-sector atrophy, heterochromia iridis, sympathetic ophthalmitis, and phthisis bulbi may all result from severe zoster vasculitis and ischemia.[24,25,30]

4) *Glaucoma*. The marked decrease in intraocular pressure often seen with herpes zoster iritis probably follows massive necrosis of the pars plicata of the ciliary body, which caused decreased production of aqueous humor. This may be more than counterbalanced, however, by impairment of outflow by clogging of the trabecular meshwork by pigment and cellular debris, acute trabeculitis, or angle closure by formation of synechia. In any or all of these, intraocular pressure may be normal or elevated.[24,25,30]

THERAPY

Unfortunately, although effective therapy is available, the literature is confused and many regimens applied empirically are without controls and

often are ineffective. These include protamide, arsenicals, dihydroergotamine, convalescent serum, typhoid vaccine, irradiation, snake venom, antimetabolites, and corticosteroids.[2,3,24,25] Of all these, none except the antimetabolites are specifically antiviral, and even these are of questionable value. Only steroids have a well-established, if controversial, role, and suppress destructive inflammation as the infection runs its natural course.

Antivirals. The first point of controversy is the use of idoxuridine to treat herpes zoster keratitis. *In vitro* studies show that herpes zoster virus is susceptible to this drug, and there is at least one report of cure of disseminated herpes zoster in a patient with Hodgkin's disease by intravenous administration of this drug.[34] A recent study on the therapy of herpes zoster ophthalmicus by intravenous cytosine arabinoside reported apparently favorable response of the disease in three steroid-resistant patients and a possible partial response in a fourth patient with Hodgkin's disease.[34] Unfortunately, no controlled studies have determined the effect of topical antimetabolites on herpes zoster keratitis.[35-38]

Steroids. Antimetabolites may have a role with the use of topical steroids. Reports by Acers,[41] Kaufman,[40] and Giles[39] note apparent reactivation of herpes simplex keratitis during treatment of herpes zoster with topical steroids. In all cases, adding idoxuridine and reducing the amount of steroids resulted in resolution of the herpes simplex keratitis. However, none of this was confirmed by culture, and the more recent report by myself and McCulley[31] and Piebenga and Laibson[32] of the successful treatment of herpes zoster dendritic keratitis by topical steroids alone suggests that some of the earlier cases actually may have been herpes zoster, not herpes simplex keratitis, and that idoxuridine prophylaxis against simplex superinfection is not always necessary.[24,25,31,32,39-41]

Similarly, in 1967 Berghaust reported 45 cases of herpes zoster ophthalmicus treated by topical steroids and antibiotics. Not only were corneal infiltrates and anterior uveitis in this group reduced when compared to the 25 controls not receiving steroids, but no patient receiving steroids developed such adverse side effects as herpes simplex or steroid glaucoma.[42]

As Forrest and Kaufman recently noted, zosteriform herpes simplex does occur with skin lesions and dendritic keratitis which can be confused with zoster.[43] Their two patients had been treated elsewhere unsuccessfully by steroids alone. Switching therapy to antiviral agents resulted in rapid and successful resolution of the acute disease, which suggests that if doubt

exists as to the correct diagnosis, full antiviral therapy should be employed first and steroids added later only if stromal involvement threatening the visual axis warrants such action.

The point of greatest contention at present is whether steroids should be administered systemically. In general, the literature favors systemic steroids. In 1969 Scheie studied 87 patients with herpes zoster ophthalmicus treated with topical steroids and intravenous ACTH or systemic corticosteroids.[24] He found this treatment more effective in rapid control of pain and in reducing the incidence and severity of keratitis, uveitis, and secondary glaucoma. No patient's infection disseminated; post-herpetic neuralgia developed in 16 patients; and recurrent steroid-sensitive keratitis developed in four.

These data compared favorably with those of Carter and Royds, whose use of prednisone in herpes zoster ophthalmicus reduced edema and scarring, but did not reduce postherpetic neuralgia, possibly because of relatively low doses of drugs.[44]

However, in 1964 Elliott reported the treatment of herpes zoster with very high doses of prednisone. His 16 patients (11 with truncal, two with geniculate, and three with ophthalmic disease) were given 60 mg. per day at any time from one to 10 days after onset of the rash. Pain in the treated patient lasted only 3½ days, as compared to 3½ weeks in the 10 control patients. There were no postherpetic neuralgias in the treated group, and two among the controls. In no case was there dissemination of the disease. Elliott further noted that the earlier treatment was started the better, preferably within two weeks of onset. Initiating therapy after the sixth week did no good, presumably because scarring around the nerves had already taken place. In addition, he concluded that low doses of steroids were of no value, e.g., 15 mg. of prednisone was no better than nothing.[45]

Aligned against the proponents of systemic steroids are those who cite the work of Merselis and others, who reported 17 cases of dissemination of zoster while patients were receiving steroids. A closer look at his figures, however, reveals that 11 patients had immunologically crippling disease such as leukemia or lymphoma; of these, four died of herpes zoster. Of the six patients with no underlying illness, only two had received steroids. These six healthy patients all underwent an illness similar to chickenpox and recovered without sequelae. Other statements against the use of steroids are based primarily on the poor results found in patients with debilitating systemic disease.[46]

Because herpes zoster may cause such devastating disease, it is reasonable that the therapeutic approach be vigorous to prevent the more severe complications. The following regimen is presently recommended:

1) No drugs, except mydriatic cycloplegics with mild or no pain or ocular involvement

2) Topical steroids, prednisolone, or dexamethasone once daily to every three hours as corneal edema and iridocyclitis warrant

3) Optional idoxuridine or vidarabine ointment three times daily, with topical steroids

4) Topical antibiotics if ulcerative keratitis is present

5) Soft-contact lens and artificial tears if corneal melting ensues

6) Non-narcotic or narcotic analgesics for neuralgia during the first 10 days. If relief is not obtained, or if uveitis or pain is not controlled by topical drugs after chest roentgenogram, complete blood count, and immune status evaluation test, start:

a) Prednisolone 20 mg. by mouth three times daily for seven days
b) Then prednisolone 15 mg. by mouth twice daily for seven days
c) Then prednisolone 15 mg. by mouth once daily for seven days and continue cycloplegics and topical steroids.

KERATOPLASTY

Any cornea sufficiently scarred by herpes zoster to warrant keratoplasty for restoration of sight usually is sufficiently anesthetic (neuroparalytic) to fare poorly with surgical manipulation.[47] Epithelial defects, melting, and superinfections in the grafts are not uncommon and secondary iritis and glaucoma generally compromise any chance a graft may have of surviving very long. Occasionally one is forced to operate because of threatened perforation from melting of a trophic epithelial defect. Keratoplasty may be successful in the presence of herpes simplex keratitis, but not of herpes zoster. Although it probably will cause marked reduction in vision for an indefinite period, a conjunctival flap is a better and far safer procedure for melting herpes zoster defects.

REFERENCES

1. Pavan-Langston, D.: Diagnosis and management of herpes simplex ocular infecion. *Int. Ophthalmol. Clin. 13:* 19-36, 1975.

2. Patterson, A. and Jones, B. R.: The management of ocular herpes. *Trans. Ophthalmol. Soc. U.K. 87:*59-84, 1967.

3. Van Horn, D., Edelhauser, H., and Schultz, R.: Experimental herpes simplex keratitis. *Arch. Ophthalmol. 84:*67-75, 1970.
4. Meyer, R., Smolin, G., Hall, J., and Okumoto, M.: Effect of local corticosteroids on antibody-forming cells in the eye and draining lymph nodes. *Invest. Ophthalmol. 14:*138-44, 1975.
5. Robbins, R. and Galin, M.: A model for steroid effects in herpes keratitis. *Arch. Ophthalmol. 93:*828, 1975.
6. Kaufman, H.: Epithelial erosion syndrome: Metaherpetic keratitis. *Am. J. Ophthalmol. 57:*984-87, 1964.
7. Pavan-Langston, D. and Nesburn, A. B.: The chronology of primary herpes simplex infection of the eye and adnexal glands. *Arch. Ophthalmol. 80:* 254-69, 1968.
8. Dawson, C., Togni, B., and Moore, T., Jr.: Structural changes in chronic herpetic keratitis. *Arch. Ophthalmol. 79:*740-47, 1968.
9. Pavan-Langston, D.: Recovery of herpes simplex virus in a case of necrotis interstitial keratitis. Unpublished.
10. Weiss, N. and Jones, B. R.: Problems of corneal grafting in herpetic keratitis. *Ciba Foundation Symp. 15:*220, 1973.
11. Henson, D., Helmsen, R., Becker, K., et al: Ultrastructural localization of herpes simplex virus antigens on rabbit corneal cells using anti-human IGG, anti-horse ferretin hybrid antibodies. *Invest. Ophthalmol. 13:*819-27, 1974.
12. Aronson, S. and Moore, T., Jr.: Corticosteroid therapy in central stromal keratitis. *Am. J. Ophthalmol. 67:*873-96, 1969.
13. Meyers, R. L., and Pettit, T.: Corneal immune response to herpes simplex virus antigens. *J. Immunol. 110:* 1575-90, 1973.
14. Kibrick, S., Tackaharski, G., Liebowitz, H., and Laibson, P.: Local corticosteroid therapy and reactivation of herpetic keratitis. *Arch. Ophthalmol. 86:*694-98, 1971.
15. Jones, D. B.: Ocular infections and therapy. *Eye Foundation of America,* Louisiana State Med. Coll. April 2, 1975, New Orleans.
16. Cavanagh, H. D.: Herpetic ocular disease: Management of inflammation associated with disciform keratitis and herpetic keratouveitis. *Int. Ophthalmol. Clinics, 15:*67-88, 1975.
17. Pavan-Langston, D. and Brockhurst, R.: Herpes simplex panuveitis. A clinical report. *Arch. Ophthalmol. 81:* 783-87, 1969.
18. Collin, B. and Abelson, M.: Herpes simplex virus in retrocorneal membrane and vitreous. In preparation.
19. Pavan-Langston, D., Dohlman, C., Geary, P., and Sulcheski, D.: Intraocular penetration of Ara-A and IDU. Therapeutic implications in herpetic uveitis. *Trans. Am. Acad. Ophthalmol. Otolaryngol. 77:*455-66, 1973.
20. Pavan-Langston, D.: Clinical evaluation of adenine arabinoside and idoxuridine in the treatment of ocular herpes simplex. *Am. J. Ophthalmol. 80:*495-502, 1975.
21. Pavan-Langston, D. and Buchanan, R.: Vidarabine therapy of simple and IDU-complicated herpetic keratitis. *Trans. Am. Acad. Ophthalmol. Otolaryngol. 81:*813-23, 1976.
22. Abel, R., Jr., Kaufman, H., and Sugan, J.: Intravenous adenine arabinoside against herpes simplex keratouveitis in humans. *Am. J. Ophthalmol. 79:*659-64, 1975.
23. Langston, R., Pavan-Langston, D., and Dohlman, C.: Penetrating keratoplasty for herpetic keratitis. *Trans. Am. Acad. Ophthalmol. Otolaryngol. 79:*577-83, 1975.
24. Scheie, H. G.: Herpes zoster ophthalmicus. *Trans. Ophthalmol. Soc. U.K. 90:*899, 1970.
25. Pavan-Langston, D.: Varicella zoster ophthalmicus. *Int. Ophthalmol. Clinics 15:*171-86, 1975.
26. Duke-Elder, S.: The Varicella-Zoster Virus. In: *Systems of Ophthalmology.* London, Kimpton, 1965, vol. 7, p. 356.
27. Edgerton, A. E.: Herpes zoster ophthalmicus. Report of cases and review of the literature. *Arch. Ophthalmol 34:*40, 114, 1945.
28. Freiwald, M.: Herpes zoster ophthal-

micus. *Med. Times 96:*43, 1968.
29. Thomas, M., Robertson, W.: Derminal transmission of a virus as a cause of shingles. *Lancet 2:*1338-49, 1968.
30. Naumann, G., Gass, D., and Font, R.: Histopathology of herpes zoster. *Am. J. Ophthalmol. 65:*533, 1968.
31. Pavan-Langston, D. and McCulley, J.: Herpes zoster dendritic keratitis. *Arch. Ophthamol. 89:*25, 1973.
32. Piebenga, L. and Laibson, P.: Dendritic lesions in herpes zoster ophthalmicus. *Arch. Ophthalmol. 90:*268, 1973.
33. Pavan-Langston, D. Unpublished data.
34. Waltuch, G. and Sachs, F.: Herpes zoster in a patient with Hodgkin's disease. *Arch. Intern. Med. 121:*458, 1971.
35. Dauber, R.: Idoxuridine in herpes zoster (DMS O) topical therapy. *Br. Med. J. 2:*526, 1974.
36. Fortuny, I., Weiss, R., and Theologides K. B.: Cytosine arabinoside in herpes zoster. *Lancet 1:*38, 1973.
37. Mann, J.: Cytosine arabinoside and herpes zoster. *Lancet 2:*166, 1971.
38. Pierce, L. and Jenkins, R.: Herpes zoster ophthalmicus treated with cytarabine. *Arch. Ophthalmol. 89:*21, 1973.
39. Giles, C.: Coexisting herpes zoster and herpes simplex. Ocular involvement. *Eye, Ear, Nose, Throat Monthly 48:* 216, 1969.
40. Kaufman, H., Dohlman, C. H., and Martola, E. L.: Herpes simplex treatment with IDU and corticosteroids. *Arch. Ophthalmol. 69:*468, 1963.
41. Acers, T. and Vaile, V.: Coexistent herpes zoster and herpes simplex. *Am. J. Ophthalmol. 63:*992, 1967.
42. Berghaust, B. and Westerby, R.: Zoster ophthalmicus — local treatment with cortisone. *Acta Ophthalmol. 45:* 787, 1967.
43. Forrest, W. M. and Kaufman, H. E.: Zosteriform herpes simplex. *Am. J. Ophthalmol. 81:*86-8, 1976.
44. Carter, A. and Royds, J.: Systemic steroids in herpes zoster. *Br. Med. J. 2:*746, 1957.
45. Elliott, F. A.: Treatment of herpes zoster with high doses of prednisone. *Lancet 2:*610, 1964.
46. Merselis, J., Kaye, D., and Hook, E.: Disseminated herpes zoster. *Arch. Intern. Med. 113:*679, 1961.
47. Dohlman, C. H.: Personal communication, June 12, 1975.